Bicillin® C-R 900/300

(penicillin G benzathine and penicillin G procaine injectable suspension)

TUBEX® 2 mL

for deep **IM** injection only

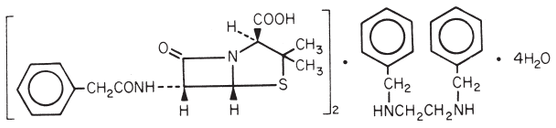
WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

℞ **only**

DESCRIPTION

Bicillin C-R 900/300 (penicillin G benzathine and penicillin G procaine injectable suspension) contains the equivalent of 900,000 units of penicillin G as the benzathine and 300,000 units of penicillin G as the procaine salts. It is available for deep intramuscular injection.

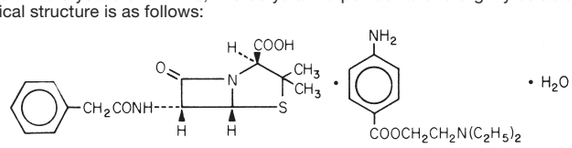
Penicillin G benzathine is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as (2*S*, 5*R*, 6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N,N'*-dibenzylethylenediamine (2:1), tetrahydrate. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol. Its chemical structure is as follows:



Molecular Formula: $(C_{16}H_{18}N_2O_4S)_2 \bullet C_{16}H_{20}N_2 \bullet 4H_2O$

Molecular Wt.: 981.19

Penicillin G procaine, (2*S*, 5*R*, 6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with 2-(diethylamino)ethyl *p*-aminobenzoate (1:1) monohydrate, is an equimolar salt of procaine and penicillin G. It occurs as white crystals or a white, microcrystalline powder and is slightly soluble in water. Its chemical structure is as follows:



Molecular Formula: $C_{16}H_{18}N_2O_4S \bullet C_{13}H_{20}N_2O_2 \bullet H_2O$

Molecular Wt.: 588.72

Each **TUBEX®** cartridge (2 mL size) contains the equivalent of 1,200,000 units of penicillin G as follows: penicillin G benthazine equivalent to 900,000 units of penicillin G and penicillin G procaine equivalent to 300,000 units of penicillin G in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Bicillin C-R 900/300 injectable suspension in **TUBEX** formulation is viscous and opaque. Read **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine and penicillin G procaine have a low solubility and, thus, the drugs are slowly released from intramuscular injection sites. The drugs are hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but more prolonged than other parenteral penicillins. Intramuscular administration of 1,200,000 units of Bicillin C-R 900/300 in patients weighing 100 to 140 lbs. usually produces average blood levels of 0.24 units/mL at 24 hours, 0.039 units/mL at seven days, and 0.024 units/mL at 10 days.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia species, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc susceptibility is used, a 10-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

Bicillin C-R 900/300 is indicated in the treatment of infections as described below that are susceptible to serum levels characteristic of this particular dosage form. Therapy should be guided by bacteriological studies (including susceptibility testing) and by clinical response.

Bicillin C-R 900/300 is indicated in the treatment of the following in pediatric patients:

Moderately severe to severe infections of the upper-respiratory tract, scarlet fever, erysipelas, and skin and soft-tissue infections due to susceptible streptococci.

NOTE: Streptococci in Groups A, C, G, H, L, and M are very susceptible to penicillin G. Other groups, including Group D (enterococci), are resistant. Penicillin G sodium or potassium is recommended for streptococcal infections with bacteremia.

Moderately severe pneumonia and otitis media due to susceptible pneumococci.

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, peritonitis, and arthritis of pneumococcal etiology are better treated with penicillin G sodium or potassium during the acute stage.

When high, sustained serum levels are required, penicillin G sodium or potassium, either IM or IV, should be used. This drug should not be used in the treatment of venereal diseases, including syphilis, gonorrhea, yaws, bejel, and pinta.

CONTRAINDICATIONS

A previous hypersensitivity reaction to any penicillin or to procaine is a contraindication.

WARNINGS

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The combination of penicillin G benzathine and penicillin G procaine should only be prescribed for the indications listed in this insert.

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN C-R 900/300, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN C-R 900/300 SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Method of Administration

Do not inject into or near an artery or nerve.

Injection into or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin C-R 900/300 and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] (See **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections.)

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. (See **DOSAGE AND ADMINISTRATION** section.)

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

PRECAUTIONS

General

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage. (See **WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections.)

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 mL of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare, or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, the drug should be discontinued and appropriate measures taken.

Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

In prolonged therapy with penicillin, and particularly with high-dosage schedules, periodic evaluation of the renal and hematopoietic systems is recommended.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine and penicillin G procaine are administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with these drugs.

Pediatric Use

(See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.)

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic cortico-steroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilatation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Streptococcal Infections

Group A infections of the upper-respiratory tract, skin and soft-tissue infections, scarlet fever, and erysipelas: A single injection of Bicillin C-R 900/300 is usually sufficient for the treatment of Group A streptococcal infections in pediatric patients.

Pneumococcal Infections (except pneumococcal meningitis)

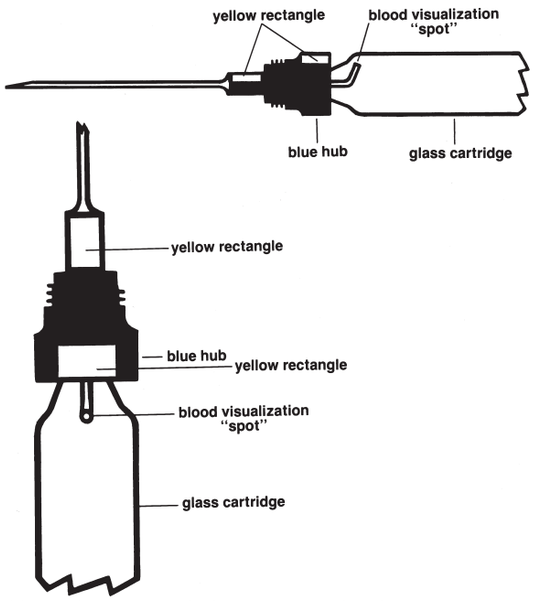
One **TUBEX** Bicillin C-R 900/300 repeated at 2- or 3-day intervals until the temperature is normal for 48 hours. Other forms of penicillin may be necessary for severe cases.

Method of Administration

Bicillin C-R 900/300 is intended for Intramuscular Injection ONLY. Do not inject into or near an artery or nerve, or intravenously or admix with other intravenous solutions. (See **WARNINGS** section).

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

The **TUBEX®** cartridge for this product incorporates several features that are designed to facilitate the visualization of blood on aspiration if a blood vessel is inadvertently entered.



The design of this cartridge is such that blood which enters its needle will be quickly visualized as a red or dark-colored "spot." This "spot" will appear on the barrel of the glass cartridge immediately proximal to the blue hub. The **TUBEX** is designed with two orientation marks, in order to determine where this "spot" can be seen. First insert and secure the cartridge in the **TUBEX** injector in the usual fashion. Locate the yellow rectangle at the base of the blue hub. This yellow rectangle is aligned with the blood visualization "spot." An imaginary straight line, drawn from this yellow rectangle to the shoulder of the glass cartridge, will point to the area on the cartridge where the "spot" can be visualized. When the needle cover is removed, a second yellow rectangle will be visible. The second yellow rectangle is also aligned with the blood visualization "spot" to assist the operator in locating this "spot." If the 2 mL metal or plastic syringe is used, the glass cartridge should be rotated by turning the plunger of the syringe clockwise until the yellow rectangle is visualized. If the 1 mL metal syringe is used, it will not be possible to continue to rotate the glass cartridge clockwise once it is properly engaged and fully threaded; it can, however, then be rotated counterclockwise as far as necessary to properly orient the yellow rectangles and locate the observation area. (In this same area in some cartridges, a dark spot may sometimes be visualized prior to injection. This is the proximal end of the needle and does not represent a foreign body in, or other abnormality of, the suspension.)

Thus, before the needle is inserted into the selected muscle, it is important for the operator to orient the yellow rectangles so that any blood which may enter after needle insertion and during aspiration can be visualized in the area on the cartridge where it will appear and not be obscured by any obstructions.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the neck of the glass **TUBEX** cartridge immediately proximal to the blue plastic needle hub for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered—only a mixture of blood and Bicillin C-R 900/300. The appearance of any discoloration is reason to withdraw the needle and discard the **TUBEX**. If it is elected to inject at another site, a new **TUBEX** cartridge should be used. If no blood or discoloration appears, inject the contents of the **TUBEX** slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some **TUBEX** cartridges may contain a small air bubble which should be disregarded, since it does not affect administration of the product. DO NOT clear any air bubbles from the cartridge or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Bicillin® C-R 900/300 (penicillin G benzathine and penicillin G procaine injectable suspension) is supplied in 2 mL size **TUBEX®** Sterile Cartridge-Needle Units in packages of 10 **TUBEX®** as follows:

1,200,000 units per **TUBEX®** (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-144-10.

1,200,000 units per **TUBEX®** (21 gauge, thin-wall 1-1/4 inch needle),

NDC 61570-143-10.

Store in a refrigerator, 2° to 8°C (36° to 46°F).

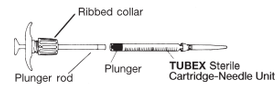
Keep from freezing.

PLEASE NOTE: THE METAL TUBEX HYPODERMIC SYRINGE AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR.
EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

NOTE: The TUBEX Injector is REUSABLE: do not discard.

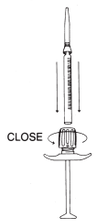
DIRECTIONS FOR USE:
BEFORE PROCEEDING, SEE IMPORTANT INFORMATION UNDER DOSAGE AND ADMINISTRATION SECTION.



NOTE: USE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

To load a TUBEX Sterile Cartridge-Needle Unit into the TUBEX Injector

1. Turn the ribbed collar to the "OPEN" position until it stops.

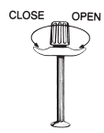


2. Hold the Injector with the open end up and fully insert the **TUBEX** Sterile Cartridge-Needle Unit.
Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the **TUBEX** Sterile Cartridge-Needle Unit until slight resistance is felt.

The Injector is now ready for use in the usual manner.

To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX Injector



1. Turn the ribbed collar to the "OPEN" position until it stops.

2. Hold the Injector with the open end up and fully insert the E.S.I. **DOSETTE** Sterile Cartridge-Needle Unit.
Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the E.S.I. **DOSETTE** Sterile Cartridge-Needle Unit until slight resistance is felt.

4. Engage the needle-cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.
The Injector is now ready for use in the usual manner.

To administer TUBEX/DOSETTE Sterile Cartridge-Needle Units
Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To remove the empty TUBEX/DOSETTE Cartridge-Needle Unit and dispose into a vertical needle disposal container

1. Do not recap the needle. Disengage the plunger rod.
2. Hold the Injector, needle down, over a vertical needle disposal container and loosen the ribbed collar. **TUBEX/DOSETTE** Cartridge-Needle Unit will drop into the container.
3. Discard the needle cover.

To remove the empty TUBEX/DOSETTE Cartridge-Needle Unit and dispose into a horizontal (mailbox) needle disposal container

1. Do not recap the needle. Disengage the plunger rod.
2. Open the horizontal (mailbox) needle disposal container. Insert **TUBEX/DOSETTE** Cartridge-Needle Unit, needle pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; **TUBEX/DOSETTE** Cartridge-Needle Unit will drop into the container.
3. Discard the needle cover.

The **TUBEX** Injector is reusable and should not be discarded.

Used **TUBEX/DOSETTE** Cartridge-Needle Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduated markings on **TUBEX/DOSETTE** Sterile Cartridge-Needle Units are to be used only as a guide in administering doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units other than TUBEX or E.S.I. DOSETTE Cartridge-Needle Units in the TUBEX Injector.

TUBEX is a registered trademark of Wyeth-Ayerst Laboratories.

REFERENCES

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3. DARBY, C. et al: Ischemia following an intragluteal injection of benzathine-procaine penicillin G mixture in a one-year-old boy. *Clin. Pediatrics, 12:*485, 1973.
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9. SCHANZER, H. et al: Accidental intra-arterial injection of penicillin G. *JAMA, 242:*1289, 1979.

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Monarch Pharmaceuticals®

CI 4658-4 Revised April 2002

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Bicillin® C-R

(penicillin G benzathine and penicillin G procaine injectable suspension)

Disposable Syringe 4 mL

for deep **IM** injection only

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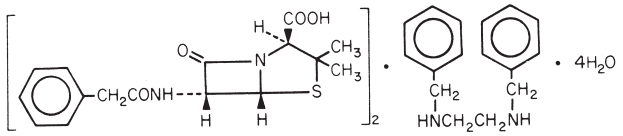
℞ only

DESCRIPTION

Bicillin C-R (penicillin G benzathine and penicillin G procaine injectable suspension) contains equal amounts of the benzathine and procaine salts of penicillin G. It is available for deep intramuscular injection.

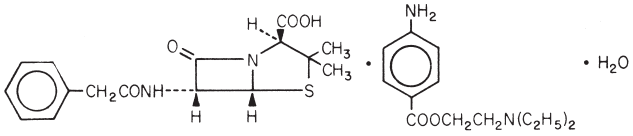
Penicillin G benzathine is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as (2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid compound with *N,N*-dibenzylethylenediamine (2:1), tetrahydrate. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol. Its chemical structure is as follows:



Molecular Formula: $(C_{16}H_{18}N_2O_4S)_2 \bullet C_{16}H_{20}N_2 \bullet 4H_2O$

Molecular Wt.: 981.19

Penicillin G procaine, (2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid compound with 2-(diethylamino)ethyl *p*-aminobenzoate (1:1) monohydrate, is an equimolar salt of procaine and penicillin G. It occurs as white crystals or a white, microcrystalline powder and is slightly soluble in water. Its chemical structure is as follows:



Molecular Formula: $C_{16}H_{18}N_2O_4S \bullet C_{13}H_{20}N_2O_2 \bullet H_2O$

Molecular Wt.: 588.72

Each disposable syringe (4 mL size) contains the equivalent of 2,400,000 units of penicillin G comprising: the equivalent of 1,200,000 units of penicillin G as the benzathine salt and the equivalent of 1,200,000 units of penicillin G as the procaine salt in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Bicillin C-R injectable suspension in the disposable-syringe formulation is viscous and opaque. Read **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine and penicillin G procaine have a low solubility and, thus, the drugs are slowly released from intramuscular injection sites. The drugs are hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but more prolonged than other parenteral penicillins.

Intramuscular administration of 600,000 units of Bicillin C-R in adults usually produces peak blood levels of 1.0 to 1.3 units per mL within 3 hours; this level falls to an average concentration of 0.32 units per mL at 12 hours, 0.19 units per mL at 24 hours, and 0.03 units per mL at seven days.

Intramuscular administration of 1,200,000 units of Bicillin C-R in adults usually produces peak blood levels of 2.1 to 2.6 units per mL within 3 hours; this level falls to an average concentration of 0.75 units per mL at 12 hours, 0.28 units per mL at 24 hours, and 0.04 units per mL at seven days.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Bacillus anthracis*, Clostridia species, *Actinomyces bovis*, *Streptobacillus moniliformis*, *Listeria mono-cytogenes*, and Leptospira species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc susceptibility is used, a 10-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

This drug is indicated in the treatment of moderately severe infections due to penicillin-G-susceptible microorganisms that are susceptible to serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including susceptibility testing) and by clinical response.

Bicillin C-R is indicated in the treatment of the following in adults and pediatric patients:

Moderately severe to severe infections of the upper-respiratory tract, scarlet fever, erysipelas, and skin and soft-tissue infections due to susceptible streptococci.

NOTE: Streptococci in Groups A, C, G, H, L, and M are very sensitive to penicillin G. Other groups, including Group D (enterococci), are resistant. Penicillin G sodium or potassium is recommended for streptococcal infections with bacteremia.

Moderately severe pneumonia and otitis media due to susceptible pneumococci.

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, peritonitis, and arthritis of pneumococcal etiology are better treated with penicillin G sodium or potassium during the acute stage.

When high, sustained serum levels are required, penicillin G sodium or potassium, either IM or IV, should be used. This drug should not be used in the treatment of venereal diseases, including syphilis, gonorrhea, yaws, bejel, and pinta.

CONTRAINDICATIONS

A previous hypersensitivity reaction to any penicillin or to procaine is a contraindication.

WARNINGS

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

The combination of penicillin G benzathine and penicillin G procaine should only be prescribed for the indications listed in this insert.

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN C-R, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN C-R SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Method of Administration

Do not inject into or near an artery or nerve.

Injection into or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin C-R and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] (See **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections.)

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. (See DOSAGE AND ADMINISTRATION section.)

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

PRECAUTIONS

General

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage. (See **WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections.)

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 mL of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare, or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, the drug should be discontinued and appropriate measures taken.

Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

In prolonged therapy with penicillin, and particularly with high-dosage schedules, periodic evaluation of the renal and hematopoietic systems is recommended.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine and penicillin G procaine are administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with these drugs.

Pediatric Use

(See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.)

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Psuedomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilatation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Streptococcal Infections Group A—Infections of the upper-respiratory tract, skin and soft-tissue infections, scarlet fever, and erysipelas.

The following doses are recommended:

Adults and pediatric patients over 60 lbs. in weight: 2,400,000 units.

Pediatric patients from 30 to 60 lbs.: 900,000 units to 1,200,000 units.

Pediatric patients under 30 lbs.: 600,000 units.

NOTE: Treatment with the recommended dosage is usually given at a single session using multiple IM sites when indicated. An alternative dosage schedule may be used, giving one-half (1/2) the total dose on day 1 and one-half (1/2) on day 3. This will also insure the penicillinemia required over a 10-day period; however, this alternate schedule should be used only when the physician can be assured of the patient's cooperation.

Pneumococcal Infections (except pneumococcal meningitis)

600,000 units in pediatric patients and 1,200,000 units in adults, repeated every 2 or 3 days until the temperature is normal for 48 hours. Other forms of penicillin may be necessary for severe cases.

Method of Administration

Bicillin C-R is intended for Intramuscular Injection ONLY. Do not inject into or near an artery or nerve, or intravenously or admix with other intravenous solutions. (See **WARNINGS** section).

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

The disposable syringe for this product incorporates several features that are designed to facilitate its use.

A single, small indentation, or "dot," has been punched into the metal ring that surrounds the neck of the syringe near the base of the needle. It is important that this "dot" be placed in a position so that it can be easily visualized by the operator following the intramuscular insertion of the syringe needle.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the syringe immediately proximal to the location of the "dot" for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered—only a mixture of blood and Bicillin C-R. The appearance of any discoloration is reason to withdraw the needle and discard the syringe. If it is elected to inject at another site, a new syringe should be used. If no blood or discoloration appears, inject the contents of the syringe slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some disposable syringes may contain a small air bubble which should be disregarded, since it does not affect administration of the product. DO NOT clear any air bubbles from the disposable syringe or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension) is supplied in packages of 10 disposable syringes as follows:

4 mL size, containing 2,400,000 units per syringe (18 gauge x 2 inch needle), NDC 61570-142-10.

Store in a refrigerator, 2° to 8°C (36° to 46°F).

Keep from freezing.

Also Available

Bicillin C-R (penicillin G benzathine and penicillin G procaine injectable suspension) is also available in packages of 10 **TUBEX®** Sterile Cartridge-Needle Units as follows:

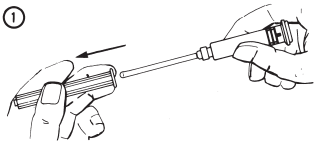
1 mL size, containing 600,000 units per **TUBEX®** (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-139-10.

2 mL size, containing 1,200,000 units per **TUBEX®** (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-141-10.

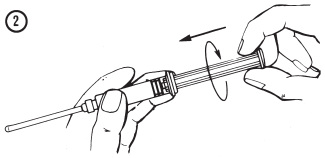
2 mL size, containing 1,200,000 units per **TUBEX®** (21 gauge, thin-wall 1-1/4 inch needle), NDC 61570-140-10.

Directions for Use of Disposable Syringes

Detach ribbed plastic cylinder from needle hub and remove from needle cover.

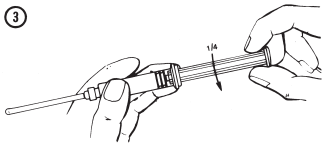


The plastic cylinder now serves as a plunger rod. To engage, place self-threading narrow end of plunger rod against metal bushing protruding from the stopper of the syringe barrel and exert gentle inward pressure while turning clockwise.



Twist plunger rod clockwise until threads are locked, then release one-quarter turn.

Sterility may be assured by not removing the needle cover until ready to make the injection.



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2. KNOWLES, J.: Accidental intra-arterial injection of penicillin. *Am. J. Dis. Child., 111*:552, 1966.
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9. SCHANZER, H. et al: Accidental intra-arterial injection of penicillin G. *JAMA, 242*:1289, 1979.

Distributed by: Monarch Pharmaceuticals, Inc.; Bristol, TN 37620
Manufactured by: Wyeth Laboratories; Philadelphia, PA 19101

Monarch Pharmaceuticals®

CI 4263-4

Revised April 2002

Bicillin® C-R

(penicillin G benzathine and penicillin G procaine injectable suspension)

TUBEX® 1 mL and 2 mL

for deep **IM** injection only

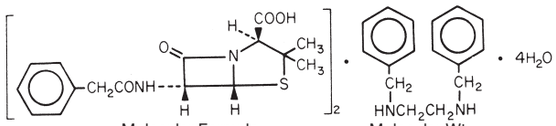
WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

℞ only

DESCRIPTION

Bicillin C-R (penicillin G benzathine and penicillin G procaine injectable suspension) contains equal amounts of the benzathine and procaine salts of penicillin G. It is available for deep intramuscular injection.

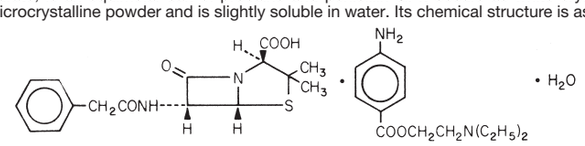
Penicillin G benzathine is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as (2*S*, 5*R*, 6*R*)-3,3-Dimethyl- 7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N,N'*-dibenzylethylenediamine (2:1), tetrahydrate. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol. Its chemical structure is as follows:



Molecular Formula: $(C_{16}H_{18}N_2O_4S)_2 \bullet C_{16}H_{20}N_2 \bullet 4H_2O$

Molecular Wt.: 981.19

Penicillin G procaine, (2*S*, 5*R*, 6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with 2-(diethylamino)ethyl p-aminobenzoate (1:1) monohydrate, is an equimolar salt of procaine and penicillin G. It occurs as white crystals or a white, microcrystalline powder and is slightly soluble in water. Its chemical structure is as follows:



Molecular Formula: $C_{16}H_{18}N_2O_4S \bullet C_{13}H_{20}N_2O_2 \bullet H_2O$

Molecular Wt.: 588.72

Each **TUBEX**® cartridge (1 mL size) contains the equivalent of 600,000 units of penicillin G comprising: the equivalent of 300,000 units penicillin G as the benzathine salt and the equivalent of 300,000 units penicillin G as the procaine salt in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Each **TUBEX** cartridge (2 mL size) contains the equivalent of 1,200,000 units of penicillin G comprising: the equivalent of 600,000 units of penicillin G as the benzathine salt and the equivalent of 600,000 units of penicillin G as the procaine salt in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Bicillin C-R injectable suspension in the **TUBEX** formulation is viscous and opaque. Read **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine and penicillin G procaine have a low solubility and, thus, the drugs are slowly released from intramuscular injection sites. The drugs are hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but more prolonged than other parenteral penicillins.

Intramuscular administration of 600,000 units of Bicillin C-R in adults usually produces peak blood levels of 1.0 to 1.3 units per mL within 3 hours; this level falls to an average concentration of 0.32 units per mL at 12 hours, 0.19 units per mL at 24 hours, and 0.03 units per mL at seven days.

Intramuscular administration of 1,200,000 units of Bicillin C-R in adults usually produces peak blood levels of 2.1 to 2.6 units per mL within 3 hours; this level falls to an average concentration of 0.75 units per mL at 12 hours, 0.28 units per mL at 24 hours, and 0.04 units per mL at seven days.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia species, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc susceptibility is used, a 10-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

This drug is indicated in the treatment of moderately severe infections due to penicillin-G-susceptible microorganisms that are susceptible to serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including susceptibility testing) and by clinical response.

Bicillin C-R is indicated in the treatment of the following in adults and pediatric patients:

Moderately severe to severe infections of the upper-respiratory tract, scarlet fever, erysipelas, and skin and soft-tissue infections due to susceptible streptococci.

NOTE: Streptococci in Groups A, C, G, H, L, and M are very sensitive to penicillin G. Other groups, including Group D (enterococci), are resistant. Penicillin G sodium or potassium is recommended for streptococcal infections with bacteremia.

Moderately severe pneumonia and otitis media due to susceptible pneumococci.

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, peritonitis, and arthritis of pneumococcal etiology are better treated with penicillin G sodium or potassium during the acute stage.

When high, sustained serum levels are required, penicillin G sodium or potassium, either IM or IV, should be used. This drug should not be used in the treatment of venereal diseases, including syphilis, gonorrhea, yaws, bejel, and pinta.

CONTRAINDICATIONS

A previous hypersensitivity reaction to any penicillin or to procaine is a contraindication.

WARNINGS

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

The combination of penicillin G benzathine and penicillin G procaine should only be prescribed for the indications listed in this insert.

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN C-R, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN C-R SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. *difficile* colitis.

Method of Administration

Do not inject into or near an artery or nerve.

Injection into or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin C-R and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] (See **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections.)

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. (See **DOSAGE AND ADMINISTRATION** section.)

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

PRECAUTIONS

General

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage. (See **WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections.)

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 mL of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare, or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, the drug should be discontinued and appropriate measures taken.

Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

In prolonged therapy with penicillin, and particularly with high-dosage schedules, periodic evaluation of the renal and hematopoietic systems is recommended.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine and penicillin G procaine are administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with these drugs.

Pediatric Use

(See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.)

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic cortico-steroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilatation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Streptococcal Infections Group A—Infections of the upper-respiratory tract, skin and soft-tissue infections, scarlet fever, and erysipelas.

The following doses are recommended:

Adults and pediatric patients over 60 lbs. in weight: 2,400,000 units.

Pediatric patients from 30 to 60 lbs.: 900,000 units to 1,200,000 units.

Pediatric patients under 30 lbs.: 600,000 units.

NOTE: Treatment with the recommended dosage is usually given at a single session using multiple IM sites when indicated. An alternative dosage schedule may be used, giving one-half (1/2) the total dose on day 1 and one-half (1/2) on day 3. This will also insure the penicillinemia required over a 10-day period; however, this alternate schedule should be used only when the physician can be assured of the patient's cooperation.

Pneumococcal Infections (except pneumococcal meningitis)

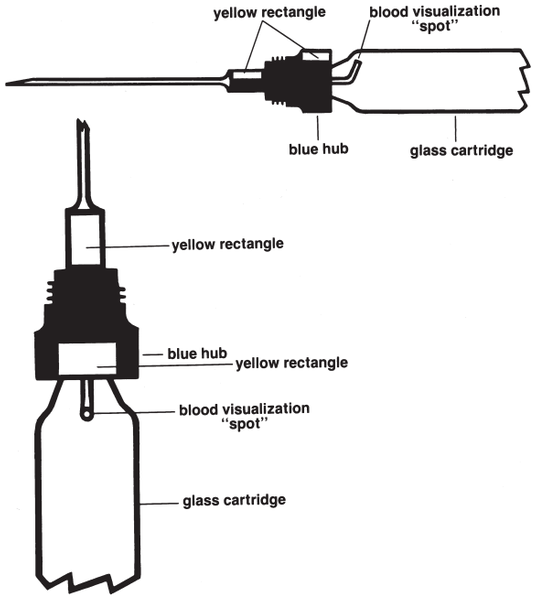
600,000 units in pediatric patients and 1,200,000 units in adults, repeated every 2 or 3 days until the temperature is normal for 48 hours. Other forms of penicillin may be necessary for severe cases.

Method of Administration

Bicillin C-R is intended for Intramuscular Injection ONLY. Do not inject into or near an artery or nerve, or intravenously or admix with other intravenous solutions. (See **WARNINGS** section).

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

The **TUBEX**® cartridge for this product incorporates several features that are designed to facilitate the visualization of blood on aspiration if a blood vessel is inadvertently entered.



The design of this cartridge is such that blood which enters its needle will be quickly visualized as a red or dark-colored "spot." This "spot" will appear on the barrel of the glass cartridge immediately proximal to the blue hub. The **TUBEX** is designed with two orientation marks, in order to determine where this "spot" can be seen. First insert and secure the cartridge in the **TUBEX** injector in the usual fashion. Locate the yellow rectangle at the base of the blue hub. This yellow rectangle is aligned with the blood visualization "spot." An imaginary straight line, drawn from this yellow rectangle to the shoulder of the glass cartridge, will point to the area on the cartridge where the "spot" can be visualized. When the needle cover is removed, a second yellow rectangle will be visible. The second yellow rectangle is also aligned with the blood visualization "spot" to assist the operator in locating this "spot." If the 2 mL metal or plastic syringe is used, the glass cartridge should be rotated by turning the plunger of the syringe clockwise until the yellow rectangle is visualized. If the 1 mL metal syringe is used, it will not be possible to continue to rotate the glass cartridge clockwise once it is properly engaged and fully threaded; it can, however, then be rotated counterclockwise as far as necessary to properly orient the yellow rectangles and locate the observation area. (In this same area in some cartridges, a dark spot may sometimes be visualized prior to injection. This is the proximal end of the needle and does not represent a foreign body in, or other abnormality of, the suspension.)

Thus, before the needle is inserted into the selected muscle, it is important for the operator to orient the yellow rectangles so that any blood which may enter after needle insertion and during aspiration can be visualized in the area on the cartridge where it will appear and not be obscured by any obstructions.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the neck of the glass **TUBEX** cartridge immediately proximal to the blue plastic needle hub for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered—only a mixture of blood and Bicillin C-R. The appearance of any discoloration is reason to withdraw the needle and discard the **TUBEX**. If it is elected to inject at another site, a new **TUBEX** cartridge should be used. If no blood or discoloration appears, inject the contents of the **TUBEX** slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some **TUBEX** cartridges may contain a small air bubble which should be disregarded, since it does not affect administration of the product. DO NOT clear any air bubbles from the cartridge or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension) is supplied in packages of 10 **TUBEX**® Sterile Cartridge-Needle Units as follows:

1 mL size, containing 600,000 units per **TUBEX**® (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-139-10.

2 mL size, containing 1,200,000 units per **TUBEX**® (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-141-10.

2 mL size, containing 1,200,000 units per **TUBEX**® (21 gauge, thin-wall 1-1/4 inch needle), NDC 61570-140-10.

Store in a refrigerator, 2° to 8°C (36° to 46°F).

Keep from freezing.

Also Available

Bicillin C-R (penicillin G benzathine and penicillin G procaine injectable suspension) is also available in packages of 10 disposable syringes as follows:

4 mL size, containing 2,400,000 units per syringe (18 gauge x 2 inch needle), NDC 61570-142-10.

PLEASE NOTE: THE METAL TUBEX HYPODERMIC SYRINGE AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR.
EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

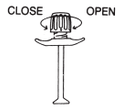
TUBEX® Injector

NOTE: The TUBEX Injector is REUSABLE: do not discard.

DIRECTIONS FOR USE:
BEFORE PROCEEDING, SEE IMPORTANT INFORMATION UNDER DOSAGE AND ADMINISTRATION SECTION.

NOTE: USE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

To load a TUBEX Sterile Cartridge-Needle Unit into the TUBEX Injector



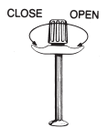
1. Turn the ribbed collar to the "OPEN" position until it stops.

2. Hold the Injector with the open end up and fully insert the **TUBEX** Sterile Cartridge-Needle Unit.
Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the **TUBEX** Sterile Cartridge-Needle Unit until slight resistance is felt.

The Injector is now ready for use in the usual manner.

To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX Injector



1. Turn the ribbed collar to the "OPEN" position until it stops.

2. Hold the Injector with the open end up and fully insert the E.S.I. **DOSETTE** Sterile Cartridge-Needle Unit.
Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the E.S.I. **DOSETTE** Sterile Cartridge-Needle Unit until slight resistance is felt.

4. Engage the needle-cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.
The Injector is now ready for use in the usual manner.

To administer TUBEX/DOSETTE Sterile Cartridge-Needle Units
Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To remove the empty TUBEX/DOSETTE Cartridge-Needle Unit and dispose into a vertical needle disposal container

1. Do not recap the needle. Disengage the plunger rod.

2. Hold the Injector, needle down, over a vertical needle disposal container and loosen the ribbed collar. **TUBEX/DOSETTE** Cartridge-Needle Unit will drop into the container.

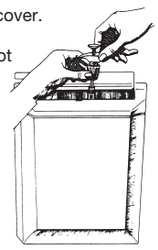
3. Discard the needle cover.

To remove the empty TUBEX/DOSETTE Cartridge-Needle Unit and dispose into a horizontal (mailbox) needle disposal container

1. Do not recap the needle. Disengage the plunger rod.

2. Open the horizontal (mailbox) needle disposal container. Insert **TUBEX/DOSETTE** Cartridge-Needle Unit, needle pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; **TUBEX/DOSETTE** Cartridge-Needle Unit will drop into the container.

3. Discard the needle cover.



The **TUBEX** Injector is reusable and should not be discarded.

Used **TUBEX/DOSETTE** Cartridge-Needle Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduated markings on **TUBEX/DOSETTE** Sterile Cartridge-Needle Units are to be used only as a guide in administering doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units other than TUBEX or E.S.I. DOSETTE Cartridge-Needle Units in the TUBEX Injector.

TUBEX is a registered trademark of Wyeth-Ayerst Laboratories.

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Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Wyeth Laboratories, Philadelphia, PA 19101

Monarch Pharmaceuticals®

CI 4657-4 Revised April 2002

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

2,400,000 units per 4 mL disposable syringe

18 gauge
2 inch needle

NDC 61570-142-10

Made and printed in USA
UK 9266-6

NDC 61570-142-10

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

FOR DEEP **IM** INJECTION **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

2,400,000 units per 4 mL

Ten sterile single-dose disposable syringes (4 mL size)

℞ only

Monarch Pharmaceuticals®

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

2,400,000 units per 4 mL disposable syringe
18 gauge
2 inch needle

UK 9266-6
UK 9266-6
UK 9266-6

2,400,000 units per 4 mL disposable syringe

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

FPO
3 61570 14210 2

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

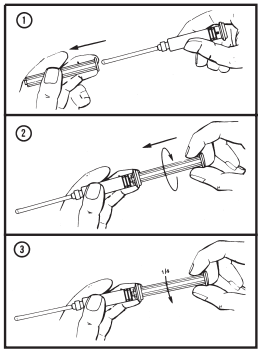
2,400,000 units per 4 mL disposable syringe

FOR DEEP **IM** INJECTION **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

Directions for Use of Disposable Syringes:



① Detach ribbed plastic cylinder from needle hub and remove from needle cover.

② The plastic cylinder now serves as a plunger rod. To engage, place self-threading narrow end of plunger rod against metal bushing protruding from the stopper of the syringe barrel and exert gentle inward pressure while turning clockwise.

③ Twist plunger rod clockwise until threads are locked, then release one-quarter turn.

Sterility may be assured by not removing the needle cover until ready to make the injection.

Each syringe (4 mL size) contains 1,200,000 units penicillin G benzathine and 1,200,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Usual Dosage: See enclosed information

Store in a refrigerator, 2° to 8° C (36° to 46° F)
Keep from freezing

Each disposable syringe includes one sterile hypodermic needle (18 gauge, 2 inch)

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Wyeth Laboratories, Philadelphia, PA 19101

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

2,400,000 units per 4 mL disposable syringe

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL

FOR DEEP **IM** INJECTION **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

Each **TUBEX®** (2 mL size) contains 600,000 units penicillin G benzathine and 600,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Usual Dosage: See enclosed information

Store in a refrigerator, 2° to 8° C (36° to 46° F)
Keep from freezing

Each **TUBEX** Sterile Cartridge-Needle Unit includes one sterile **TUBEX** hypodermic needle (21 gauge, thin-wall 1¼ inch needle)

Made and printed in USA

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Wyeth Laboratories, Philadelphia, PA 19101

UK 22139-3

UK 22139-3
UK 22139-3
UK 22139-3

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

21 gauge, thin-wall 1¼ inch needle

NDC 61570-140-10

NDC 61570-140-10

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

FOR DEEP **IM** INJECTION **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

1,200,000
units per 2 mL

Ten Tubex® (2 mL size) ℞only

Monarch Pharmaceuticals®

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

1,200,000
units per 2 mL
21 gauge, thin-wall 1¼ inch needle

1,200,000 units per 2 mL

Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)

FPO
3 61570 14010 8

LOT
EXP
To be inserted by laboratory

Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL

FOR DEEP **IM** INJECTION **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

Each **TUBEX®** (2 mL size) contains 900,000 units penicillin G benzathine and 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Usual Dosage: See enclosed information

Store in a refrigerator, 2° to 8° C (36° to 46° F)
Keep from freezing

Each **TUBEX** Sterile Cartridge-Needle Unit includes one sterile **TUBEX** hypodermic needle (21 gauge, thin-wall 1¼ inch needle)

Made and printed in USA

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Wyeth Laboratories, Philadelphia, PA 19101

UK 22046-3

UK 22046-3
UK 22046-3

Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

21 gauge, thin-wall 1¼ inch needle

NDC 61570-143-10

NDC 61570-143-10

Bicillin® C-R 900/300

(penicillin G benzathine and penicillin G procaine injectable suspension)

FOR DEEP **IM** INJECTION **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

1,200,000
units per 2 mL

Ten Tubex® (2 mL size)

℞ only

Monarch Pharmaceuticals®

Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000
units per 2 mL
21 gauge, thin-wall 1¼ inch needle

Bicillin® C-R 900/300 1,200,000 units per 2 mL
(penicillin G benzathine and penicillin G procaine injectable suspension)

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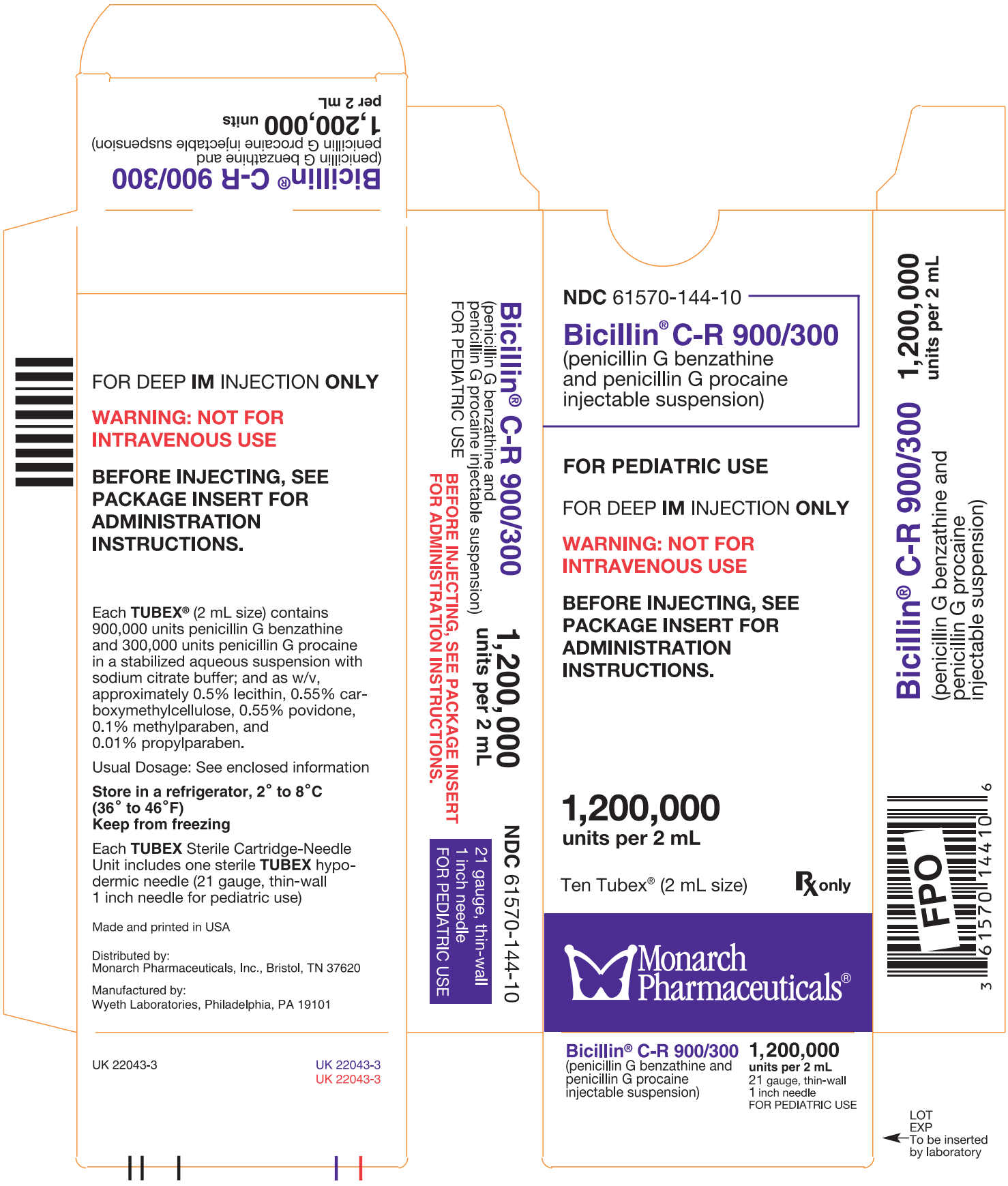
3 61570 14310 9

LOT
EXP
To be inserted by laboratory



Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL

FOR DEEP IM INJECTION ONLY

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

Each TUBEX® (2 mL size) contains 900,000 units penicillin G benzathine and 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Usual Dosage: See enclosed information

Store in a refrigerator, 2° to 8°C (36° to 46°F)
Keep from freezing

Each TUBEX Sterile Cartridge-Needle Unit includes one sterile TUBEX hypodermic needle (21 gauge, thin-wall 1 inch needle for pediatric use)

Made and printed in USA

Distributed by:
Monarch Pharmaceuticals, Inc., Bristol, TN 37620

Manufactured by:
Wyeth Laboratories, Philadelphia, PA 19101

UK 22043-3

UK 22043-3
UK 22043-3

Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL
FOR PEDIATRIC USE
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
21 gauge, thin-wall
1 inch needle
FOR PEDIATRIC USE
NDC 61570-144-10

NDC 61570-144-10

Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)

FOR PEDIATRIC USE

FOR DEEP IM INJECTION ONLY

WARNING: NOT FOR INTRAVENOUS USE

BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.

1,200,000
units per 2 mL

Ten Tubex® (2 mL size)

℞only

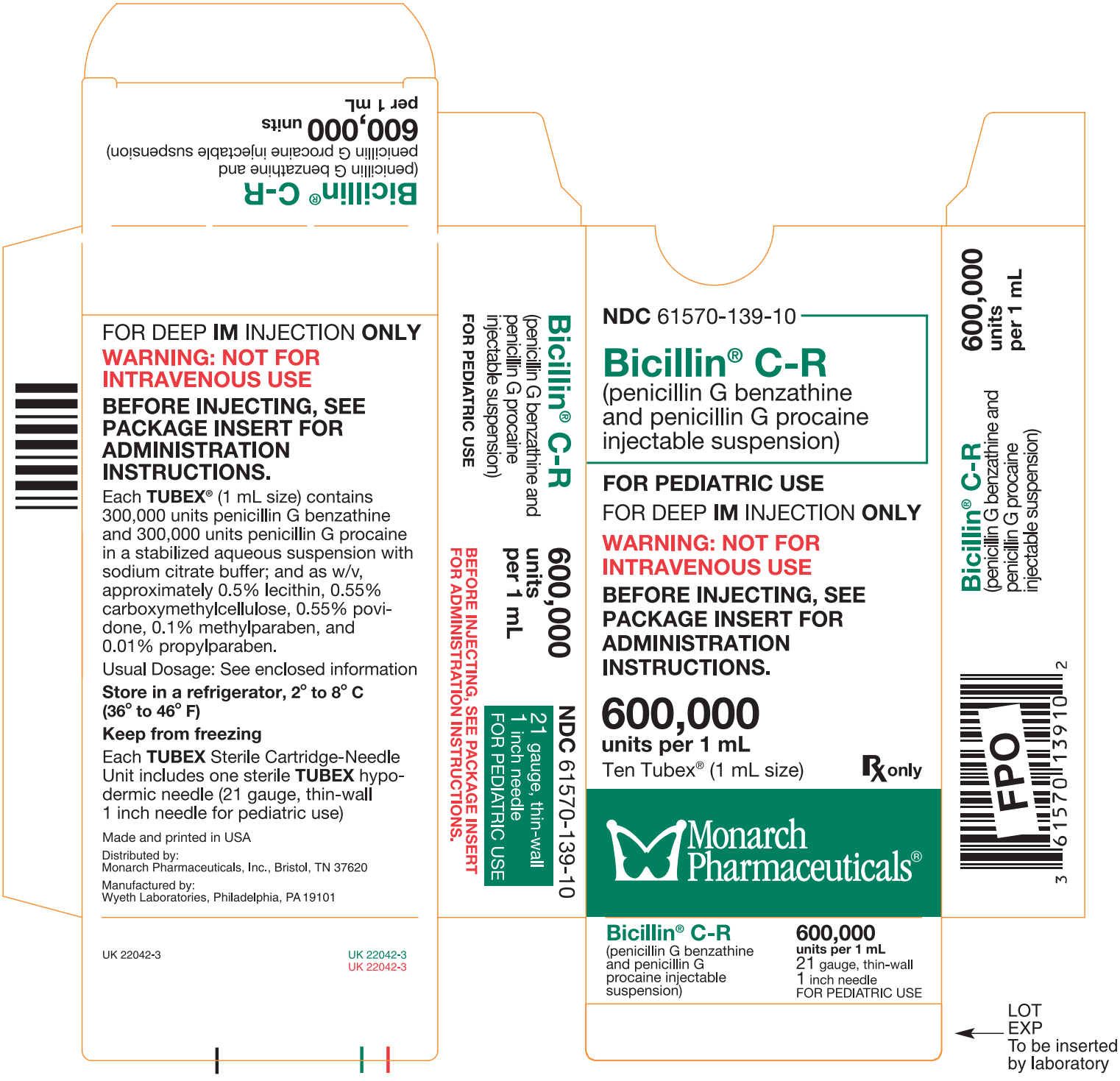
Monarch Pharmaceuticals®

Bicillin® C-R 900/300
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000
units per 2 mL
21 gauge, thin-wall
1 inch needle
FOR PEDIATRIC USE

Bicillin® C-R 900/300 1,200,000 units per 2 mL
(penicillin G benzathine and penicillin G procaine injectable suspension)

FPO
3 61570 14410 6

LOT
EXP
To be inserted by laboratory


Bicillin® C-R
(penicillin G benzathine and
penicillin G procaine injectable suspension)
600,000 units per 1 mL
FOR DEEP IM INJECTION ONLY
WARNING: NOT FOR INTRAVENOUS USE
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
Each TUBEX® (1 mL size) contains 300,000 units penicillin G benzathine and 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.
Usual Dosage: See enclosed information
Store in a refrigerator, 2° to 8° C (36° to 46° F)
Keep from freezing
Each TUBEX Sterile Cartridge-Needle Unit includes one sterile TUBEX hypodermic needle (21 gauge, thin-wall 1 inch needle for pediatric use)
Made and printed in USA
Distributed by:
Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by:
Wyeth Laboratories, Philadelphia, PA 19101
UK 22042-3
UK 22042-3
UK 22042-3
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
600,000 units per 1 mL
FOR PEDIATRIC USE
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
NDC 61570-139-10
21 gauge, thin-wall 1 inch needle
FOR PEDIATRIC USE
NDC 61570-139-10
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
FOR PEDIATRIC USE
FOR DEEP IM INJECTION ONLY
WARNING: NOT FOR INTRAVENOUS USE
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
600,000 units per 1 mL
Ten Tubex® (1 mL size)
℞ only
Monarch Pharmaceuticals®
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
600,000 units per 1 mL
21 gauge, thin-wall
1 inch needle
FOR PEDIATRIC USE
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
600,000 units per 1 mL
FPO
3 61570 13910 2
LOT
EXP
To be inserted by laboratory


Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL
FOR DEEP IM INJECTION ONLY
WARNING: NOT FOR INTRAVENOUS USE
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
Each TUBEX® (2 mL size) contains 600,000 units penicillin G benzathine and 600,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer; and as w/v, approximately 0.5% lecithin, 0.55% carboxymethylcellulose, 0.55% povidone, 0.1% methylparaben, and 0.01% propylparaben.
Usual Dosage: See enclosed information
Store in a refrigerator, 2° to 8° C (36° to 46° F)
Keep from freezing
Each TUBEX Sterile Cartridge-Needle Unit includes one sterile TUBEX hypodermic needle (21 gauge, thin-wall 1 inch needle for pediatric use)
Made and printed in USA
Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Wyeth Laboratories, Philadelphia, PA 19101
UK 22041-3
UK 22041-3
UK 22041-3
UK 22041-3
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
FOR PEDIATRIC USE
1,200,000 units per 2 mL
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
21 gauge, thin-wall 1 inch needle FOR PEDIATRIC USE
NDC 61570-141-10
NDC 61570-141-10
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
FOR PEDIATRIC USE
FOR DEEP IM INJECTION ONLY
WARNING: NOT FOR INTRAVENOUS USE
BEFORE INJECTING, SEE PACKAGE INSERT FOR ADMINISTRATION INSTRUCTIONS.
1,200,000 units per 2 mL
Ten Tubex® (2 mL size)
℞ only
Monarch Pharmaceuticals®
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
1,200,000 units per 2 mL
21 gauge, thin-wall 1 inch needle FOR PEDIATRIC USE
1,200,000 units per 2 mL
Bicillin® C-R
(penicillin G benzathine and penicillin G procaine injectable suspension)
FPO
3 61570 14110 5
LOT
EXP
To be inserted by laboratory

BICILLIN® C-R 900/300

(900,000 units penicillin G benzathine and 300,000 units penicillin G procaine injectable suspension)

1,200,000 UNITS per 2 mL

FOR DEEP
IM INJECTION
ONLY

WARNING:
NOT FOR INTRA-VENOUS USE

Dist. By: Monarch Pharm., Inc.
Bristol, TN

TL364-3 TUBEX®

EXP

SAMPLE

BICILLIN® C-R

(300,000 units penicillin G benzathine and 300,000 units penicillin G procaine injectable suspension)

600,000 UNITS per 1 mL

WARNING: NOT FOR INTRAVENOUS USE

FOR DEEP **IM** USE **ONLY**

EXP

Dist. By: Monarch Pharm., Inc., Bristol, TN

TUBEX®

TL363-3

SAMPLE

BICILLIN® C-R

(600,000 units penicillin G benzathine and 600,000 units penicillin G procaine injectable suspension)

1,200,000 UNITS per 2 mL

FOR DEEP
IM INJECTION
ONLY

WARNING:
NOT FOR INTRA-VENOUS USE

Dist. By: Monarch Pharm., Inc.
Bristol, TN

TL362-3 TUBEX®

EXP

SAMPLE

BICILLIN® C-R

(penicillin G benzathine and penicillin G procaine injectable suspension in equal portions)

2,400,000 UNITS per 4 mL

FOR DEEP **IM** USE **ONLY**

WARNING: NOT FOR INTRAVENOUS USE

Dist. By: Monarch Pharm., Inc., Bristol, TN

TL163-5

6157014201

EXP

SAMPLE

BICILLIN® C-R

(penicillin G benzathine and penicillin G procaine injectable suspension in equal portions)

1,200,000 UNITS per 2 mL

FOR DEEP
IM INJECTION
ONLY

WARNING:
NOT FOR INTRA-VENOUS USE

Dist. By: Monarch Pharm., Inc.
Bristol, TN

TL153-6 TUBEX®

EXP

SAMPLE

BICILLIN® C-R 900/300

(900,000 units penicillin G benzathine and 300,000 units penicillin G procaine injectable suspension)

1,200,000 UNITS per 2 mL

FOR DEEP
IM INJECTION
ONLY

WARNING:
NOT FOR INTRA-VENOUS USE

Dist. By: Monarch Pharm., Inc.
Bristol, TN

TL128-5 TUBEX®

EXP

SAMPLE

Bicillin® L-A

(penicillin G benzathine injectable suspension)

TUBEX® 1 mL and 2 mL

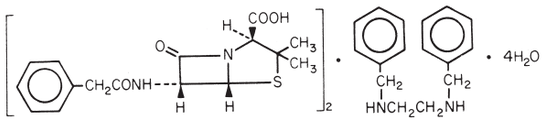
for deep **IM** injection only

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

℞ only

DESCRIPTION

Bicillin L-A (penicillin G benzathine injectable suspension) is available for deep intramuscular injection. Penicillin G benzathine is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as (2*S*, 5*R*, 6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N,N'*-dibenzylethylenediamine (2:1), tetrahydrate. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol. Its chemical structure is as follows:



Molecular Formula
$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2 \cdot 4H_2O$

Molecular Wt.
981.19

Bicillin L-A contains penicillin G benzathine in aqueous suspension with sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Bicillin L-A injectable suspension in **TUBEX®** formulation is viscous and opaque. It is available in 1 mL and 2 mL **TUBEX®** Sterile Cartridge-Needle Units containing the equivalent of 600,000 units and 1,200,000 units respectively of penicillin G as the benzathine salt. Read **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION** sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine has an extremely low solubility and, thus, the drug is slowly released from intramuscular injection sites. The drug is hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Intramuscular administration of 300,000 units of penicillin G benzathine in adults results in blood levels of 0.03 to 0.05 units per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 600,000 units and for 14 days following administration of 1,200,000 units. Blood concentrations of 0.003 units per mL may still be detectable 4 weeks following administration of 1,200,000 units.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia species, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc susceptibility is used, a 20-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

Intramuscular penicillin G benzathine is indicated in the treatment of infections due to penicillin-G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine:

Mild-to-moderate infections of the upper-respiratory tract due to susceptible streptococci.

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Penicillin G Benzathine Therapy is Indicated as Prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as follow-up prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNINGS

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

Penicillin G benzathine should only be prescribed for the indications listed in this insert.

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN L-A CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN L-A SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Method of Administration

Do not inject into or near artery or nerve.

Injection in or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin L-A and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] (See **PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION** sections.)

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. (See **DOSAGE AND ADMINISTRATION** section.)

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

PRECAUTIONS

General

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage. (See **WARNINGS,** and **DOSAGE AND ADMINISTRATION** sections.)

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with this drug.

Pediatric Use

(See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.)

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine, although a causal relationship has not necessarily been established:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilatation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Streptococcal (Group A) Upper-respiratory Infections (for example, pharyngitis)

Adults – a single injection of 1,200,000 units; older pediatric patients – a single injection of 900,000 units; infants and pediatric patients under 60 lbs. – 300,000 to 600,000 units.

Syphillis

Primary, secondary, and latent – 2,400,000 units (1 dose). Late (tertiary and neurosyphilis) – 2,400,000 units at 7-day intervals for three doses.

Congenital – under 2 years of age: 50,000 units/kg/body weight; ages 2 to 12 years: adjust dosage based on adult dosage schedule.

Yaws, Bejel, and Pinta – 1,200,000 units (1 injection).

Prophylaxis – for rheumatic fever and glomerulonephritis.

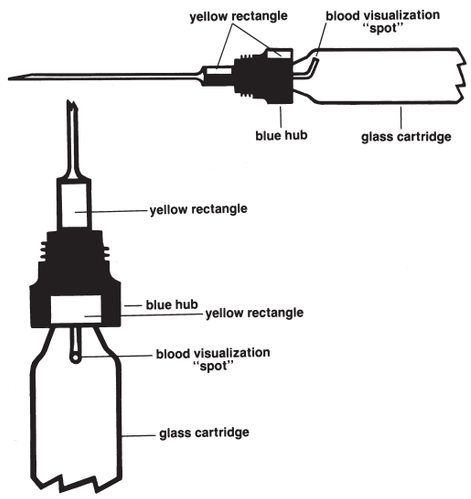
Following an acute attack, penicillin G benzathine (parenteral) may be given in doses of 1,200,000 units once a month or 600,000 units every 2 weeks.

Method of Administration

Bicillin L-A is intended for Intramuscular Injection ONLY. Do not inject into or near an artery or nerve, or intravenously or admix with other intravenous solutions. (See **WARNINGS** section).

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

The **TUBEX**® cartridge for this product incorporates several features that are designed to facilitate the visualization of blood on aspiration if a blood vessel is inadvertently entered.



The design of this cartridge is such that blood which enters its needle will be quickly visualized as a red or dark-colored "spot." This "spot" will appear on the barrel of the glass cartridge immediately proximal to the blue hub. The **TUBEX** is designed with two orientation marks, in order to determine where this "spot" can be seen. First insert and secure the cartridge in the **TUBEX** injector in the usual fashion. Locate the yellow rectangle at the base of the blue hub. This yellow rectangle is aligned with the blood visualization "spot." An imaginary straight line, drawn from this yellow rectangle to the shoulder of the glass cartridge, will point to the area on the cartridge where the "spot" can be visualized. When the needle cover is removed, a second yellow rectangle will be visible. The second yellow rectangle is also aligned with the blood visualization "spot" to assist the operator in locating this "spot." If the 2 mL metal or plastic syringe is used, the glass cartridge should be rotated by turning the plunger of the syringe clockwise until the yellow rectangle is visualized. If the 1 mL metal syringe is used, it will not be possible to continue to rotate the glass cartridge clockwise once it is properly engaged and fully threaded; it can, however, then be rotated counterclockwise as far as necessary to properly orient the yellow rectangles and locate the observation area. (In this same area in some cartridges, a dark spot may sometimes be visualized prior to injection. This is the proximal end of the needle and does not represent a foreign body in, or other abnormality of, the suspension.)

Thus, before the needle is inserted into the selected muscle, it is important for the operator to orient the yellow rectangles so that any blood which may enter after needle insertion and during aspiration can be visualized in the area on the cartridge where it will appear and not be obscured by any obstructions.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the cartridge in the area previously identified (see above) for the appearance of a red or dark-colored "spot."

Blood or "typical blood color" may *not* be seen if a blood vessel has been entered – only a mixture of blood and Bicillin L-A. The appearance of any discoloration is reason to withdraw the needle and discard the glass **TUBEX** cartridge. If it is elected to inject at another site, a new cartridge should be used. If no blood or discoloration appears, inject the contents of the cartridge slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some **TUBEX** cartridges may contain a small air bubble which should be disregarded, since it does not affect administration of the product. DO NOT clear any air bubbles from the cartridge or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

How Supplied

Bicillin® L-A (penicillin G benzathine injectable suspension) is supplied in packages of 10 **TUBEX**® Sterile Cartridge-Needle Units as follows:

1 mL size, containing 600,000 units per **TUBEX**® (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-146-10.

2 mL size, containing 1,200,000 units per **TUBEX**® (21 gauge, thin-wall 1-1/4 inch needle), NDC 61570-147-10.

Store in a refrigerator, 2° to 8°C (36° to 46°F).

Keep from freezing.

Also Available

Bicillin L-A (penicillin G benzathine injectable suspension) is also available in packages of 10 disposable syringes as follows:

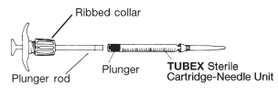
4 mL size, containing 2,400,000 units per syringe (18 gauge x 2 inch needle), NDC 61570-148-10.

PLEASE NOTE: THE METAL TUBEX HYPODERMIC SYRINGE AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

NOTE: The TUBEX Injector is REUSABLE: do not discard.

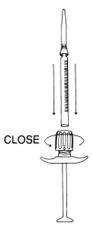
DIRECTIONS FOR USE: BEFORE PROCEEDING, SEE IMPORTANT INFORMATION UNDER DOSAGE AND ADMINISTRATION SECTION.



NOTE: USE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

To load a TUBEX Sterile Cartridge-Needle Unit into the TUBEX Injector

1. Turn the ribbed collar to the "OPEN" position until it stops.



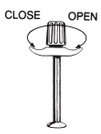
2. Hold the Injector with the open end up and fully insert the **TUBEX** Sterile Cartridge-Needle Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the **TUBEX** Sterile Cartridge-Needle Unit until slight resistance is felt.

The Injector is now ready for use in the usual manner.

To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX Injector



1. Turn the ribbed collar to the "OPEN" position until it stops.

2. Hold the Injector with the open end up and fully insert the E.S.I. **DOSETTE** Sterile Cartridge-Needle Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the E.S.I. **DOSETTE** Sterile Cartridge-Needle Unit until slight resistance is felt.

4. Engage the needle-cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.

The Injector is now ready for use in the usual manner.

To administer TUBEX/DOSETTE Sterile Cartridge-Needle Units

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To remove the empty TUBEX/DOSETTE Cartridge-Needle Unit and dispose into a vertical needle disposal container

1. Do not recap the needle. Disengage the plunger rod.

2. Hold the Injector, needle down, over a vertical needle disposal container and loosen the ribbed collar. **TUBEX/DOSETTE** Cartridge-Needle Unit will drop into the container.

3. Discard the needle cover.

To remove the empty TUBEX/DOSETTE Cartridge-Needle Unit and dispose into a horizontal (mailbox) needle disposal container

1. Do not recap the needle. Disengage the plunger rod.

2. Open the horizontal (mailbox) needle disposal container. Insert **TUBEX/DOSETTE** Cartridge-Needle Unit, needle pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; **TUBEX/DOSETTE** Cartridge-Needle Unit will drop into the container.

3. Discard the needle cover.

The **TUBEX** Injector is reusable and should not be discarded.

Used **TUBEX/DOSETTE** Cartridge-Needle Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduated markings on **TUBEX/DOSETTE** Sterile Cartridge-Needle Units are to be used only as a guide in administering doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units other than TUBEX or E.S.I. DOSETTE Cartridge-Needle Units in the TUBEX Injector.

TUBEX is a registered trademark of Wyeth-Ayerst Laboratories.

REFERENCES

1. SHAW, E.: Transverse myelitis from injection of penicillin. *Am. J. Dis. Child., 111:*548, 1966.
2. KNOWLES, J.: Accidental intra-arterial injection of penicillin. *Am. J. Dis. Child., 111:*552, 1966.
3. DARBY, C. et al: Ischemia following an intragluteal injection of benzathine-procaine penicillin G mixture in a one-year-old boy. *Clin. Pediatrics, 12:*485, 1973.
4. BROWN, L. & NELSON, A.: Postinfectious intravascular thrombosis with gangrene. *Arch. Surg., 94:*652, 1967.
5. BORENSTINE, J.: Transverse myelitis and penicillin (Correspondence). *Am. J. Dis. Child., 112:*166, 1966.
6. ATKINSON, J.: Transverse myelopathy secondary to penicillin injection. *J. Pediatrics, 75:*867, 1969.
7. TALBERT, J. et al: Gangrene of the foot following intramuscular injection in the lateral thigh: A case report with recommendations for prevention. *J. Pediatrics, 70:*110, 1967.
8. FISHER, T.: Medicolegal affairs. *Canad. Med. Assoc. J., 112:*395, 1975.
9. SCHANZER, H. et al: Accidental intra-arterial injection of penicillin G. *JAMA, 242:*1289, 1979.

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Wyeth Laboratories, Philadelphia, PA 19101

Monarch Pharmaceuticals®

CI 4656-5 Revised April 2002

CODE
INSERTED
HERE

Bicillin® L-A

(penicillin G benzathine injectable suspension)

Disposable Syringe

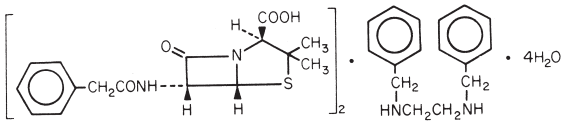
for deep **IM** injection only

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

℞ **only**

DESCRIPTION

Bicillin L-A (penicillin G benzathine injectable suspension) is available for deep intramuscular injection. Penicilin G benzathine is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as (2*S*, 5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido) -4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N,N'*-dibenzylethylenediamine (2:1), tetrahydrate. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol. Its chemical structure is as follows:



Molecular Formula
$(C_{16}H_{18}N_2O_4S)_2 \bullet C_{16}H_{20}N_2 \bullet 4H_2O$

Molecular Wt.
981.19

Bicillin L-A contains penicillin G benzathine in aqueous suspension with sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Bicillin L-A suspension in the disposable-syringe formulation is viscous and opaque. It is available in a 4 mL size containing the equivalent of 2,400,000 units of penicillin G as the benzathine salt. Read **CONTRAINDICATIONS**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine has an extremely low solubility and, thus, the drug is slowly released from intramuscular injection sites. The drug is hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Intramuscular administration of 300,000 units of penicillin G benzathine in adults results in blood levels of 0.03 to 0.05 units per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 600,000 units and for 14 days following administration of 1,200,000 units. Blood concentrations of 0.003 units per mL may still be detectable 4 weeks following administration of 1,200,000 units.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia species, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc susceptibility is used, a 20-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

Intramuscular penicillin G benzathine is indicated in the treatment of infections due to penicillin-G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine:

Mild-to-moderate infections of the upper-respiratory tract due to susceptible streptococci.

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Penicillin G Benzathine Therapy is Indicated as Prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as follow-up prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNINGS

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

Penicillin G benzathine should only be prescribed for the indications listed in this insert.

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN L-A, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN L-A SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembraneous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Method of Administration

Do not inject into or near an artery or nerve. Injection into or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin L-A and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] (See **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** sections.)

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. (See **DOSAGE AND ADMINISTRATION** section.)

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

PRECAUTIONS

General

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage. (See **WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections.)

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with this drug.

Pediatric Use

(See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.)

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilatation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Streptococcal (Group A) Upper Respiratory Infections (for example, pharyngitis)

Adults—a single injection of 1,200,000 units; older pediatric patients—a single injection of 900,000 units; infants and pediatric patients under 60 lbs.—300,000 to 600,000 units.

Syphilis

Primary, secondary, and latent—2,400,000 units (1 dose). Late (tertiary and neurosyphilis)—2,400,000 units at 7-day intervals for three doses.

Congenital—under 2 years of age: 50,000 units/kg/body weight; ages 2 to 12 years: adjust dosage based on adult dosage schedule.

Yaws, Bejel, and Pinta—1,200,000 units (1 injection).

Prophylaxis—for rheumatic fever and glomerulonephritis.

Following an acute attack, penicillin G benzathine (parenteral) may be given in doses of 1,200,000 units once a month or 600,000 units every 2 weeks.

METHOD OF ADMINISTRATION

BICILLIN L-A IS INTENDED FOR INTRAMUSCULAR INJECTION ONLY. DO NOT INJECT INTO OR NEAR AN ARTERY OR NERVE, OR INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. (SEE **WARNINGS** SECTION.)

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

The disposable syringe for this product incorporates several features that are designed to facilitate its use.

A single, small indentation, or "dot," has been punched into the metal ring that surrounds the neck of the syringe near the base of the needle. It is important that this "dot" be placed in a position so that it can be easily visualized by the operator following the intramuscular insertion of the syringe needle.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the syringe immediately proximal to the location of the "dot" for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered—only a mixture of blood and Bicillin L-A. The appearance of any discoloration is reason to withdraw the needle and discard the syringe. If it is elected to inject at another site, a new syringe should be used. If no blood or discoloration appears, inject the contents of the syringe slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some disposable syringes may contain a small air bubble which should be disregarded since it does not affect administration of this product. DO NOT clear any air bubbles from the disposable syringe or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Bicillin® L-A (penicillin G benzathine injectable suspension) is supplied in packages of 10 disposable syringes as follows:

4 mL size, containing 2,400,000 units per syringe (18 gauge x 2 inch needle), NDC 61570-148-10.

Store in a refrigerator, 2° to 8°C (36° to 46°F).

Keep from freezing.

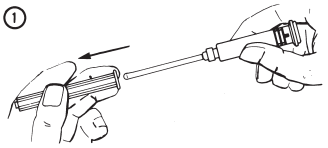
Also Available:

Bicillin L-A (penicillin G benzathine injectable suspension) is also available in packages of 10 **TUBEX**® Sterile Cartridge-Needle Units as follows:

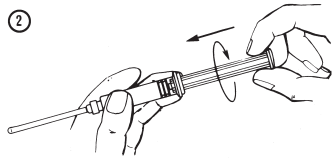
1 mL size, containing 600,000 units per **TUBEX**® (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-146-10.

2 mL size, containing 1,200,000 units per **TUBEX**® (21 gauge, thin-wall 1-1/4 inch needle), NDC 61570-147-10.

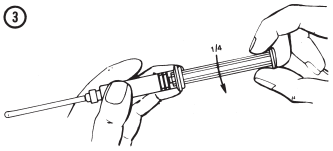
Directions for Use of Disposable Syringes



Detach ribbed plastic cylinder from needle hub and remove from needle cover.



The plastic cylinder now serves as a plunger rod. To engage, place self-threading narrow end of plunger rod against metal bushing protruding from the stopper of the syringe barrel and exert gentle inward pressure while turning clockwise.



Twist plunger rod clockwise until threads are locked, then release one-quarter turn. Sterility may be assured by not removing the needle cover until ready to make the injection.

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